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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| <b>(51) International Patent Classification <sup>5</sup> :</b><br><b>A61K 47/18, 37/34, 37/43</b>   | <b>A1</b> | <b>(11) International Publication Number:</b> <b>WO 95/01185</b><br><b>(43) International Publication Date:</b> 12 January 1995 (12.01.95)   |
| <b>(21) International Application Number:</b> PCT/SE94/00622<br><b>(22) International Filing Date:</b> 22 June 1994 (22.06.94)<br><br><b>(30) Priority Data:</b><br>084,563 29 June 1993 (29.06.93) US<br><br><b>(71) Applicant:</b> FERRING AB [SE/SE]; P.O. Box 30047, S-200 61 Malmö (SE).<br><br><b>(72) Inventors:</b> HARRIS, Alan; Sövdborgsgatan 4, S-216 19 Malmö (SE). TENNHAMMAR-EKMAN, Birgitta; Månstigen 9, S-216 19 Malmö (SE).  |           | <b>(81) Designated States:</b> BG, BR, BY, CA, CN, CZ, FI, HU, JP, KR, LV, NO, NZ, PL, RO, RU, SK, UA, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).<br><br><b>Published</b><br><i>With international search report.</i> |
| <b>(54) Title:</b> STABILIZED PHARMACEUTICAL PEPTIDE COMPOSITIONS<br><br><b>(57) Abstract</b><br><br>Disclosed is a stabilized aqueous composition for administration to a patient comprising a biologically active peptide, a buffer, a quaternary amine-type preservative or disinfectant, and an osmotic pressure-controlling agent, which composition can be stored and used at room temperature. The buffer stabilizes the pH of the composition between about 4 and 6. The preferred buffer contains citrate and/or phosphate, and the preferred preservative or disinfectant is benzalkonium chloride. The composition protects the peptide contained therein from adhering to container surfaces, particularly in containers made of polymeric materials. |           |  |

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## STABILIZED PHARMACEUTICAL PEPTIDE COMPOSITIONS.

The present invention relates to stabilized aqueous pharmaceutical compositions for nasal, oral or parenteral administration of small and medium-size peptides (up to about eicosapeptides), such as desmopressin (1-deamino-8-D-arginine vasopressin; DDAVP).

As used herein, the term "stabilized composition" refers to an aqueous solution for therapeutic use, containing at least one small or medium-size biologically active peptide. Such stabilization should allow the composition to be stored at room temperature for extended periods without loss in biological activity.

A substantial number of biologically active peptides, their derivatives and analogs (in the following termed "peptides") are known to be therapeutically useful. For various reasons they are often administered in form of aqueous compositions, that is, sterile aqueous solutions containing a known amount of peptide.

The biological activity of the peptides to be administered is often extremely high. Thus, only very small amounts of peptide are needed for a single dose. Such dilute peptide solutions in general are not stable at room temperature for longer periods, even if kept in sealed containers. The therapeutically active peptide hormone analog desmopressin is such a peptide. Its aqueous solution has to be stored at a temperature not exceeding 8° C. Storage at higher temperatures such as, for instance, room temperature, results in the degradation of desmopressin by hydrolytic and/or oxidative processes which are not blocked by the addition of a preservative, such as chlorobutanol (1,1,1-trichloro-2-methylpropan-2-ol). However, chlorobutanol effectively protects desmopressin against microbial attack.

Another problem with dilute aqueous solutions of peptides is the adsorption of minute amounts of peptide to the walls of the container in which the solution is kept. Since such peptide solutions are usually very dilute, adsorption of even minor amounts may substantially reduce the amount of peptide available for administration.

A particularly attractive way of administration of small and medium-size peptides in solution is via the nasal mucosa, either as drops or in spray form, which is even more convenient and more reproducible. Desmopressin, for instance, can be administered in an aqueous, 0.9 % sodium chloride solution (saline) by this route.

Various kinds of intranasal spray delivery devices are known in the art. In general, peptides in an aqueous solution are administered by means of metered-dose spray pumps, such as those manufactured by Ing. Erich Pfeiffer KG, Radolfzell, Germany. An alternate route is via a graduated plastic tube of special design called "rhinyle" which is partially filled with an aqueous solution containing a peptide. One end of the rhinyle is placed in the mouth and the other end is placed in the desired nostril. The solution is then delivered to the nostril by blowing.

Peptides for nasal administration often have extremely high biological activity, and only a very small amount of peptide is needed in a single dose. However, the particular form of administration may require a minimum liquid volume for good reproducibility. Thus, effective concentration ranges for nasally administered peptides are generally quite low. For instance, a single desmopressin dose for nasal administration is typically between 10  $\mu\text{g}$  to 40  $\mu\text{g}$ , but may even be as little as 2.5  $\mu\text{g}$  and as high as 300  $\mu\text{g}$ . Typical dose volumes are from 100  $\mu\text{l}$  to 400  $\mu\text{l}$  (4 x 100  $\mu\text{l}$ ). These doses are normally taken on a regular

basis, such as at least once daily.

Thus, it is an object of the present invention to overcome the aforementioned stability and storage problems associated with known aqueous solutions of small and medium size peptides, particularly of aqueous solutions containing desmopressin.

Another object is to provide a stabilized aqueous solution containing a peptide for nasal, oral or parenteral administration which can be conveniently stored at room temperature for extended periods of time, for instance, one year, without risking partial or total degradation or microbial contamination of the peptide contained therein.

A further object is to protect the peptide in solution from adhering to the walls of the container without using extraneous additives specifically designed for that purpose.

Yet another object is to provide an aqueous nasal or drop spray composition for the management of diseases and abnormal conditions which are mitigated by administration of small and medium-sized biologically active peptides.

The present invention is an aqueous composition for administration of small and medium-size peptides, particularly desmopressin, which can maintain stability over time and at room temperature, of active biological ingredients carried therein such as a peptide, an analog of a peptide or mixtures of peptides and/or their analogs. The solution contains a buffer, a quaternary amine preservative or disinfectant and an osmotic pressure-controlling agent.

The quaternary amine preservative or disinfectant

selectively used have, in addition to their namesake functions, the unexpected ability to prevent adsorption of small and medium size peptide components from adhering to container walls, particularly walls of containers made of polymeric materials.

It is preferred for the peptide or peptide analog to be oxytocin or vasopressin, or their analogs and derivatives, such as particularly preferred, desmopressin (hereinafter also "DDAVP"). Also preferred are terlipressin (N- $\alpha$ -triglycyl-8-lysine)-vasopressin), atosiban ((Mpa<sup>1</sup>, D-Tyr(Et)<sup>2</sup>, Thr<sup>4</sup>, Orn<sup>8</sup>)-oxytocin), carbetocin ((1-desamino-1-monocarba-2(0-methyl)-tyrosine)oxytocin) and triptorelin [D-Trp<sup>6</sup>]-LHRH.

It is preferred for the buffer to be capable of maintaining a pH of between 4.0 and 6.0. Especially preferred is a pH of about 5.0.

In one embodiment, the buffer used is acetic acid/sodium acetate. It is preferred for the stabilized peptide solution according to the invention to contain citrate and/or phosphate. Preferred buffer systems according to the invention are citric acid/disodium hydrogen phosphate, sodium dihydrogen phosphate/disodium hydrogen phosphate, and citric acid/sodium citrate. Specifically preferred is a buffer comprising citrate - phosphate - sodium ions in a molar ratio of from about 1 : 3 : 3 to about 1 : 1 : 2.

It is preferred for the quaternary amine preservative or disinfectant to be benzalkonium chloride, (NR<sup>1</sup>R<sup>2</sup>R<sup>3</sup>R<sup>4</sup>)<sup>+</sup>Cl<sup>-</sup>; where R<sup>1</sup>, R<sup>2</sup> = methyl, R<sup>3</sup> = benzyl, R<sup>4</sup> = C<sub>8</sub>H<sub>17</sub> to C<sub>18</sub>H<sub>37</sub>. The composition according to the invention preferably contains the quaternary amine preservative or disinfectant in a concentration from about 0.05 to about 0.2 mg per ml. Particularly preferred is a concentration of about 0.1 mg per ml.

It is preferred for the osmotic pressure-controlling agent to be sodium chloride. The buffer components also contribute substantially to osmotic pressure control.

5 According to a preferred aspect of the invention the composition additionally contains at least one mucosal absorption enhancer such as bile salts, monolauryl ethers of macrogols, phospholipids, and fusidate derivatives.

10 A preferred embodiment of the composition according to the invention contains from 0.025 mg to 1.5 mg of desmopressin acetate, from 1.35 to 1.75 mg of citric acid, from 2.25 to 2.65 mg of disodium hydrogen phosphate, from 0.05 to 0.20 mg benzalkonium chloride, and sodium chloride in an amount  
15 sufficient to provide the overall solution with an osmotic pressure comparable to that of human plasma.

According to another preferred embodiment of the invention, there is also disclosed the use of an aqueous  
20 spray composition for the management of diseases and abnormal conditions that can be treated by nasal administration of small and medium-size peptides.

FIGURE 1 graphically illustrates the results of stability  
25 testing for the compositions prepared according to the present invention.

The invention will now be explained in more detail by reference to the following experimental examples:

30

Example 1

**Preparation of test compositions.** Five test compositions containing desmopressin (DDAVP) acetate for nasal spray or  
35 drop compositions containing various preservatives were prepared, compositions A, B, C, D and E (see Table 1). Each test sample contained 0.089 mg DDAVP free base per

ml, and Table 1 denotes the typ of buffer used in each system. Millipore -filtered water was used as solvent.

Compositions A and B were prepared according to the present disclosure. Compositions C, D and E were prepared for comparative testing of other preservatives.

The stability of the known, unbuffered Minirin® (DDAVP) spray containing NaCl and chlorobutanol has a useful shelf life of 3 years at refrigerated storage when kept in sealed glass containers. It is not stable at room temperature when stored for longer periods of time. Note that composition E contains NaCl and chlorobutanol, but is a buffered solution.

Table 1

**Stabilized desmopressin compositions (amounts per ml)**

A and B denote compositions according to the invention; C, D, E denote compositions prepared for comparison

| Compo-<br>sition | NaCl<br>mg | BH<br>mg (mmol)                     | B <sup>-</sup> Na <sup>+</sup><br>mg     | Preservative<br>mg   |
|------------------|------------|-------------------------------------|--|--|
| A                | 8.74       | AcOH (mmol)<br>$2.96 \cdot 10^{-3}$ | NaOAc<br>0.58                            | benzalkonium<br>chloride, 0.1  |
| B                | 6.29       | citric acid<br>1.56                 | Na <sub>2</sub> HPO <sub>4</sub><br>2.43 | benzalkonium<br>chloride, 0.1  |
| C                | 5.24       | citric acid<br>1.97                 | Na <sub>2</sub> HPO <sub>4</sub><br>1.83 | benzyl alcohol<br>10.0   |
| D                | 6.30       | citric acid<br>1.56                 | Na <sub>2</sub> HPO <sub>4</sub><br>2.43 | methyl p-hydroxy<br>benzoate*, 0.80<br>propyl p-hydroxy-<br>benzoate**, 0.20 |
| E                | 5.64       | citric acid<br>1.97                 | Na <sub>2</sub> HPO <sub>4</sub><br>1.83 | chlorobutanol<br>5.00  |

\*methyl paraben; \*\*propyl paraben



Example 2

**Stability testing by detecting peptid d gradation.** The DDAVP-compositions prepared in Example 1 were stored in 10 ml glass vials (hydrolytic class 1, provided with Teflon® stoppers) in the dark at 65° C for up for 13 weeks. Samples were taken after 1, 2, 3, 5, 7, 9, 11, and 13 weeks and analyzed for DDAVP by HPLC [Varian Star system; Lichrospher® PR-18 5µm column (50 x 4 mm); gradient elution with various proportions of acetonitrile/0.0667 M aqueous phosphate buffer pH 7].

The results are graphically depicted in Fig. 1 and demonstrate the superior stabilizing effect of the composition according to the invention. The experimental data contained in Fig. 1 were also used for calculation of first order rate constants shown in Table 2, below.

Table 2

**First order rate constants for degradation of desmopressin**

| Composition | k (s <sup>-1</sup> )   | correlation coefficient |
|-------------|------------------------|-------------------------|
| A           | $4.6 \cdot 10^{-8}$    | 0.98                    |
| B           | $8.0 \cdot 10^{-8}$    | 0.98                    |
| C           | $1.6 \cdot 10^{-7}$    | 0.97                    |
| D           | $8.8 \cdot 10^{-8}$    | 0.96                    |
| E           | $\sim 9 \cdot 10^{-7}$ | 0.83                    |

Example 3

**Calculation of useful shelf-life.** From the slopes of the curves in Fig. 1 and from corresponding storage tests carried out at 37° C, 50° C, and 60° C Arrhenius activation

energies ( $E_a$ ) were obtained for compositions A, B, C and D. Composition E did not show Arrhenius-type behaviour since it was the least stable composition by far.

- 5 The storage time over which total DDAVP content of each composition was reduced by 10% ( $t_{90}$ ) at 25° C and 30° C, "useful shelf life", was calculated from  $E_a$  which is tabulated below in Table 3.

10 Table 3

Useful shelf life in years ( $t_{90}$ ) for stabilized desmopressin compositions

| 15 | Composition | activation energy<br>( $E_a$ , kJ/mol) | $t_{90}$ |       |
|----|-------------|--|----------|-------|
|    |             |  | 25° C    | 30° C |
|    | A           | 123.5                                  | 27.0     | 11.9  |
|    | B           | 115.1                                  | 12.9     | 6.0   |
| 20 | C           | 115.5                                  | 5.7      | 2.7   |
|    | D           | 102.8                                  | 7.4      | 3.7   |

- As Table 3 shows, desmopressin is preserved in compositions A and B for extended periods of time at room temperature, thus demonstrating the ability of the present invention to be stored and used for extensive periods without refrigeration.

30 Example 4

- Comparison of intra-nasal desmopressin uptake. 24 healthy fasting male subjects were given (randomized) desmopressin (20  $\mu$ l) intranasally in spray form (200  $\mu$ l), using either composition B or the commercially available unbuffered Minirin formulation containing chlorobutanol as preservative. Blood samples were collected at intervals

and desmopressin plasma levels monitored over a 12 h period by a desmopressin-specific RIA plasma assay (Lundin, S. et al., Acta Endocrinologica (Copenhagen) 108 (1985) 170-183). Essentially the same desmopressin plasma level profile was found for the two compositions. This is an unexpected result since H.A. Batts et al. (J. Pharm. Pharmacol. 1989, 156-159) found that chlorobutanol and benzalkonium chloride differed significantly in their effect on the mucociliary transport rate in a frog palate model. The rate of mucociliary clearance affects the comparatively slow intra-nasal uptake of peptides and other nasally administered biologically active compounds.

#### Example 5

**Absorption-blocking effect of desmopressin.** Sterile aqueous solutions of desmopressin marked with  $^{125}\text{I}$  (appr. 10,000 CPM/ml) containing benzalkonium chloride + saline, chlorobutanol + saline, or saline only, were all incubated in tubes of polystyrene, polypropylene and glass for 24 h at ambient temperature.

In the solutions containing benzalkonium chloride and chlorobutanol, respectively, desmopressin showed insignificant adsorption, whereas only about half of the amount of desmopressin in the preservative-free solution could be recovered from the plastic tubes.

While the various features and embodiments of the present invention have been described herein, it is possible that one skilled in the art could modify the various aspects of the invention and obtain the same objectives. The present disclosure contemplates such modifications as being within its spirit and scope.

C l a i m s

1. A stable, aqueous composition for administration to a patient of at least one biologically active peptide,  
5 comprising:  
a) said biologically active peptide;  
b) a buffering agent;  
c) a quaternary amine preservative or disinfectant;  
and  
10 d) an osmotic pressure-controlling agent.
2. The composition according to claim 1, wherein said peptide is oxytocin or vasopressin.
- 15 3. The composition according to claim 1, wherein said peptide is an analog or derivative of a peptide selected from the group consisting of oxytocin, vasopressin, terlipressin, atosiban, carbetocin, and triptorelin.
- 20 4. The composition according to claim 3, wherein said analog is desmopressin.
5. The composition according to claim 1, wherein said buffering agent is a buffer which maintains the pH of said  
25 composition between 4.0 and 6.0.
6. The composition according to claim 5, wherein said buffer maintains said pH at about 5.0.
- 30 7. The composition according to claim 1, wherein said buffering agent comprises a buffer selected from the group consisting of citrate, phosphate, and a mixture of citrate and phosphate.
- 35 8. The composition according to claim 7, wherein said buffer mixture of citrate and phosphate contains sodium ions such that the molar ratio of citrate, phosphate and

sodium ions is from about 1 : 3 : 3 to about 1 : 1 : 2.

9. The composition according to claim 1, wherein said quaternary amine preservative or disinfectant is

5 benzalkonium chloride having the following structure:



10 where  $R^1$  and  $R^2$  are both methyl;  $R^3$  is benzyl; and  $R^4$  can be an alkyl group from  $C_8H_{17}$  to  $C_{18}H_{37}$ .

10. The composition according to claim 1, wherein said osmotic pressure-controlling agent is sodium chloride.

15 11. The composition according to claim 1, wherein said administration is oral.

12. The composition according to claim 1, wherein said administration is parenteral.

20

13. An aqueous composition for nasal administration of a biologically active component, comprising:

- 25 a) said biologically active component selected from the group consisting of a peptide, a peptide analog and a mixture of peptides and/or peptide analogs;
- b) a buffering agent;
- c) a quaternary amine preservative or disinfectant; and
- 30 d) an osmotic pressure-controlling agent such that said composition is capable of maintaining said biologically active component in a functionally stable condition over extended periods and at room temperature.

35

14. The composition of claim 13, wherein said peptide is oxytocin or vasopressin.

15. The composition of claim 13, wherein said peptide analog is selected from the group consisting of an oxytocin analog and a vasopressin analog.

5 16. The composition of claim 15, wherein said vasopressin analog is desmopressin.

10 17. The composition according to claim 13, wherein said buffering agent is a buffer which maintains the pH of said composition between 4.0 and 6.0.

18. The composition according to claim 17, wherein said buffer maintains said pH at about 5.0.

15 19. The composition of claim 13, wherein said buffering agent comprises a buffer selected from the group consisting of citrate, phosphate, and a mixture of citrate and phosphate.

20 20. The composition of claim 19, wherein said buffer comprises a mixture of citrate and disodium hydrogen phosphate such that the molar ratio of citrate, phosphate and sodium ions is from about 1 : 3 : 3 to about 1 : 1 : 2.

25 21. The composition according to claim 13, wherein said quaternary amine preservative or disinfectant is benzalkonium chloride having the following structure:

30  $(NR^1R^2R^3R^4)^+Cl^-$

where  $R^1$  and  $R^2$  are both methyl;  $R^3$  is benzyl; and  $R^4$  can be an alkyl group from  $C_8H_{17}$  to  $C_{18}H_{37}$ .

35 22. The composition of claim 13, wherein said osmotic pressure-controlling agent is sodium chloride, said sodium chloride being added to said composition in an amount

sufficient to make said composition compatible to the osmotic pressure of human plasma.

23. A stable aqueous composition for nasal application, comprising:

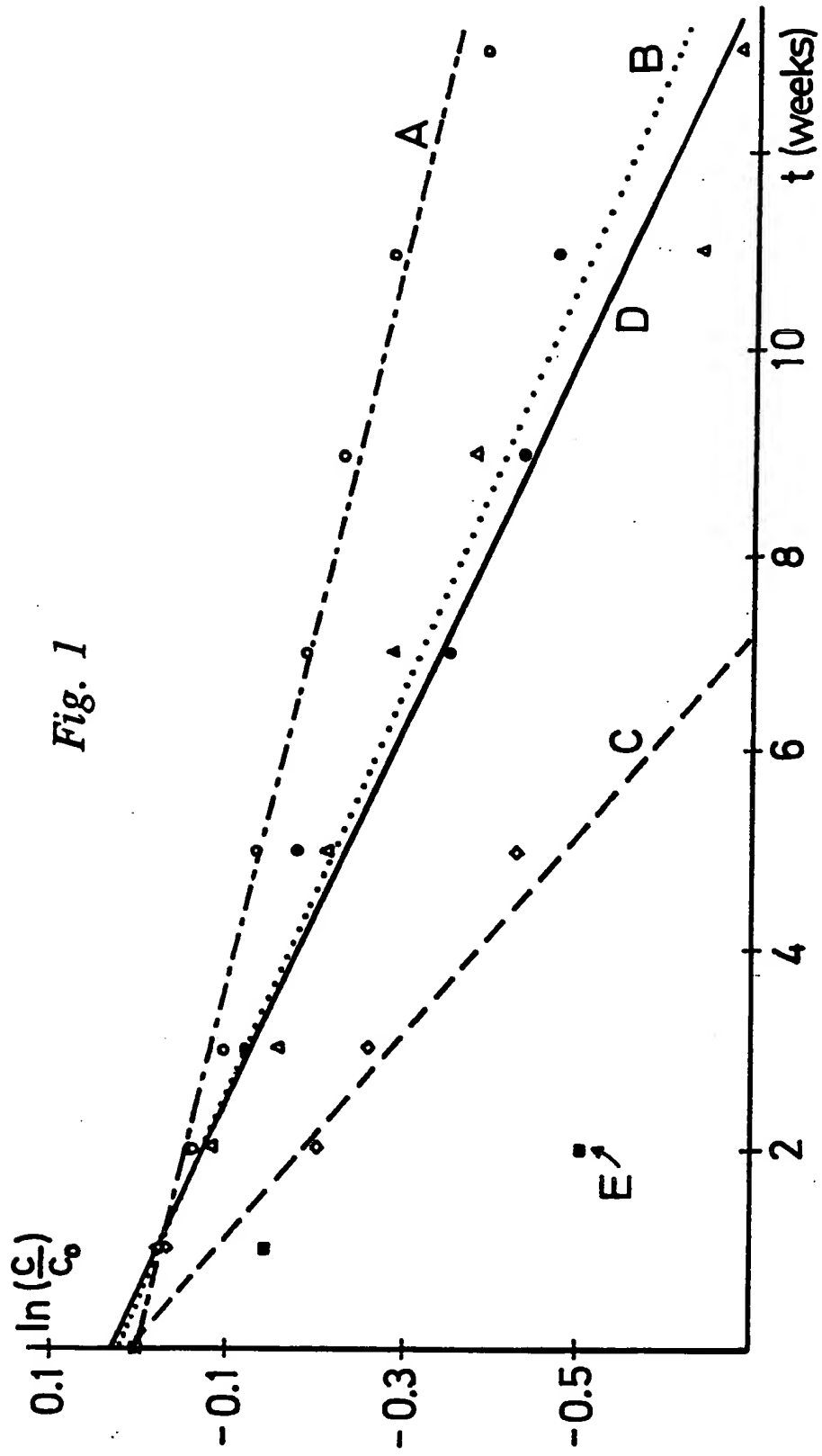
- a) from 0.025 mg to 1.5 mg of desmopressin acetate;
- b) from 1.35 mg to 1.75 mg of citric acid;
- c) from 2.25 mg to 2.65 mg of disodium hydrogen phosphate;
- d) from 0.05 mg to 0.20 mg of benzalkonium chloride; and
- e) sodium chloride in an amount sufficient to provide said composition with an osmotic pressure comparable to that of human plasma.

24. A sealed container filled with a stabilized aqueous spray composition according to claim 23 for nasal administration of said desmopressin.

25. A method of treating diseases and abnormal conditions that can be affected by the administration of small and medium-size peptides using the composition of claim 1.

26. A method of treating diseases and abnormal conditions that can be affected by the administration of small and medium-size peptides using the composition of claim 13.

27. A method of treating diseases and abnormal conditions that can be affected by the administration of small and medium size peptides using the composition of claim 23.





## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 94/00622

## A. CLASSIFICATION OF SUBJECT MATTER

IPC5: A61K 47/18, A61K 37/34, A61K 37/43

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MEDLINE, BIOSIS, EMBASE, WPI, CA, CLAIMS, JAPIO

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| X         | EP, A1, 0199992 (EISAI CO., LTD.), 5 November 1986<br>(05.11.86)<br>---            | 1-24                  |
| X         | DE, C2, 2254043 (HOECHST AG), 24 January 1985<br>(24.01.85)<br>---                 | 1-24                  |
| X         | DE, C2, 3335086 (SANDOZ-PATENT-GMBH), 20 Sept 1990<br>(20.09.90)<br>---            | 1,9-13,21,22          |
| X         | WO, A1, 9303744 (BOEHRINGER MANNHEIM GMBH),<br>4 March 1993 (04.03.93)<br>---      | 1,5-10,12             |

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search

3 October 1994

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## INTERNATIONAL SEARCH REPORT

International application N .

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## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages         | Relevant to claim No. |
|-----------|--|-----------------------|
| A         | DE, A, 1900367 (NOVO TERAPEUTISK LABORATORIUM A/S),<br>4 Sept 1969 (04.09.69)<br><br>----- | 1-22                  |

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 94/00622

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 25-27  
because they relate to subject matter not required to be searched by this Authority, namely:  
See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**  
Information on patent family members

27/08/94

International application No.

PCT/SE 94/00622

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s)  | Publication<br>date  |
|---|---------------------|---|--|
| EP-A1- 0199992                            | 05/11/86            | SE-T3- 0199992<br>CA-A- 1269205<br>JP-A- 61221125   | 22/05/90<br>01/10/86   |
| DE-C2- 2254043                            | 24/01/85            | AT-B- 329743<br>AU-A- 6215873<br>BE-A- 806911<br>CA-A- 1014470<br>FR-A,B- 2205308<br>GB-A- 1454105<br>NL-A- 7314884   | 25/05/76<br>08/05/75<br>06/05/74<br>26/07/77<br>31/05/74<br>27/10/76<br>07/05/74   |
| DE-C2- 3335086                            | 20/09/90            | AT-B- 394947<br>AU-B- 572800<br>AU-A- 1984983<br>AU-A- 2103588<br>BE-A- 897904<br>CA-A- 1220138<br>CH-A,B- 657779<br>DE-A- 3348341<br>FR-A,B- 2533826<br>GB-A,B- 2127689<br>JP-B- 3054647<br>JP-A- 59089619<br>NL-A- 8303386<br>SE-B,C- 455671<br>SE-A- 8305485 | 27/07/92<br>19/05/88<br>12/04/84<br>22/12/88<br>04/04/84<br>07/04/87<br>30/09/86<br>14/09/89<br>06/04/84<br>18/04/84<br>20/08/91<br>23/05/84<br>01/05/84<br>01/08/88<br>06/04/84 |
| WO-A1- 9303744                            | 04/03/93            | AU-A- 2409492<br>CA-A- 2115348<br>DE-A- 4126983<br>EP-A- 0528313<br>EP-A- 0607156<br>FI-A,D- 940674<br>HU-D- 9400416  | 16/03/93<br>04/03/93<br>18/02/93<br>24/02/93<br>27/07/94<br>14/02/94<br>00/00/00   |
| DE-A- 1900367                             | 04/09/69            | BE-A- 726681<br>FR-A- 2000114<br>GB-A- 1202607<br>NL-A- 6900460   | 09/07/69<br>29/08/69<br>19/08/70<br>14/07/69   |